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Autonomic disturbances and cardiovascular reflexes in idiopathic Parkinson's disease

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Summary. A total of 22 patients suffering from idiopathic Parkinson's disease and 20 age-matched volunteers were questioned about autonomic disturbances and all underwent four non-invasive tests examining cardiovascular reflexes. Significantly more autonomic disturbances were reported by the patients than by the controls. Resting blood pressure was significantly decreased in patients taking dopamine agonists, whereas it was normal in those patients who only received levodopa and anticholinergics. Resting heart rate and resting beat-to-beat variation were normal in the patients, as were the blood pressure response to standing and the postural heart rate response. No pathological response to the Valsalva manoeuvre could be detected. On the other hand, the heart rate variation evoked by deep breathing as well as the blood pressure response and the heart rate response to sustained isometric exercise were significantly diminished in the patients with idiopathic Parkinson's disease. These findings indicate a central disturbance of cardiovascular reflex control, whereas the corresponding peripheral pathways seem to be normal.

Key words: Idiopathic Parkinson's disease – Autonomic disturbances – Cardiovascular reflexes – Levodopa – Dopamine agonists

Introduction

Since its original description [19] it has been known that idiopathic Parkinson's disease may be accompanied by autonomic disturbances. Cardiovascular reflexes have been investigated by several authors [1, 2, 7, 12, 13, 15]. The results have been somewhat inconsistent, maybe as a result of the inhomogeneous composition of patient groups, which in some cases included patients with idiopathic Parkinson's disease and others with progressive autonomic failure. In the present study only patients with definite idiopathic Parkinson's disease underwent tests for cardiovascular reflex function.

Patients and methods

A total of 22 patients (12 male, 10 female) with idiopathic Parkinson's disease with a mean age of 62.2 years (SD 9.7 years) and a mean illness duration of 9.9 years (SD 5.7 years) participated in this study. The mean disability scores according to the scales of Hoehn and Yahr [14] and of Webster [28] were 2.7 (SD 0.9) and 9.8 (SD 4.7) respectively. Of these patients 21 were receiving levodopa with a decarboxylase inhibitor (benserazide; mean daily dose 705 mg), 15 dopamine agonists (bromocriptine and lisuride; mean daily doses 21.5 mg and 1 mg respectively) and 8 anticholinergics. The treatment was not discontinued for the course of the study. Patients suffering from arterial hypertension or cardiorespiratory disorders were not included, and none received any additional treatment which could have influenced the autonomic nervous system or cardiovascular function.

As controls, 20 healthy volunteers were examined. Two persons were excluded because of previously unknown arterial hypertension (resting blood pressure $>180/100$ mmHg), which was detected during our examination. The remaining 18 controls (10 male, 8 female) had a mean age of 63.6 years (SD 9.9 years). None of the volunteers had taken any medication during the 48 h preceding our study.

The persons tested were questioned as to the presence or the absence of autonomic disturbances (dizziness, fainting, disturbances of micturition, bowel dysfunction, troubled sleep, hypersalivation and sweating disturbances). No attempt was made to quantify these disturbances.

Cardiovascular reflexes were examined under standardized conditions. The ECG was continuously recorded on magnetic tape. The R-R intervals were electronically measured off-line. With the aid of a microcomputer the heart rate was calculated at the beginning of every minute from the mean of 5 R-R intervals and as a measure of the beat-to-beat variation the MCD value (mean consecutive difference) [8, 9] of 100 successive R-R intervals was determined. Blood pressure was measured by a sphygmomanometer in the right upper arm at intervals of 1 min.

For the assessment of postural blood pressure and heart rate response patients and volunteers had to remain in a supine position on a tilt table for 10 min. They were then passively brought into a vertical position within 5 s, where they maintained for another 10 min. Besides heart rate, blood pressure and MCD, the 30/15 ratio [8, 9, 10, 26] was calculated. The 30/15 ratio is the R-R interval of the 30th beat divided by the R-R interval of the 15th beat after changing position.

The respiratory influence was measured with the patient in a recumbent position. After resting for 15 min the test persons had to breathe as deeply as possible at a rate of 6/min for 2 min; this was followed by a 3-min resting period. Respiration was monitored by a nasal thermistor. The E/I ratio was calculated as an additional parameter. For the E/I ratio [25] the mean value of the longest R-R intervals during expiration is

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divided by the mean value of the shortest R-R intervals during inspiration.

For the Valsalva manoeuvre only the heart rate and the beat-to-beat variation were recorded, as our method of measuring blood pressure did not permit recognition of rapid and short-lived changes. For three periods of 10 s, at 50-s intervals, each test person was required to blow into a mouthpiece attached to a manometer at 20 mmHg and 40 mmHg respectively. The Valsalva ratio [8, 9] was calculated by dividing the longest R-R interval after blowing by the shortest R-R interval during blowing.

The isometric exercise was performed by adducting the thumb of the left hand with 30% of the maximal force for 5 min. The force was measured by a strain gauge and displayed on a screen, where it could be monitored continuously by the test person.

For the statistical evaluation a statistical program (Stats 2; Statsoft; Tulsa, Okla., USA) running on a personal computer was used.

Results

The patients reported significantly more autonomic disturbances than the controls ($P<0.001$). The individual complaints reported by the patients and the controls are listed in Table 1. The complaints concerning sexual dysfunction were too unreliable to be evaluated. The most frequent complaints concerned troubled sleep and dizziness after rising from a supine or sitting position. In neither group was there any correlation between the age of the test persons and the frequency of autonomic disturbances, nor was there any correlation with duration or severity of Parkinson's disease.

Patients' age, the autonomic disturbances reported by the patients, the duration of Parkinson's disease and the degree of disability did not correlate with the results of any of the cardiovascular reflexes described below.

Supine resting blood pressure was significantly lower in patients than in controls ($P<0.05$) (Table 2). A more detailed analysis shows that only the patients receiving dopamine agonists had a significantly diminished blood pressure ($P<0.05$), while it was normal in those taking only levodopa and anticholinergics. Dopamine agonists did not influence any of the test results described below. Resting heart rate and resting beat-to-beat variation were the same in both groups; both showed a significant correlation between heart rate and beat-to-beat variation at rest.

Postural changes of blood pressure were not significantly different between patients and controls (Table 3, Fig. 1). After standing for 5 min blood pressure reached practically the resting value. Only one patient had a postural drop of systolic pressure slightly in excess of 30 mmHg. The changes in heart rate (Fig. 2) and in beat-to-beat variation were almost identical in each group. The 30/15 ratio was not significantly different in the two groups.

During deep respiration (Table 4) beat-to-beat variation was smaller in patients than in controls without, however, reaching the level of significance ($P<0.519$). The increase in beat-to-beat variation during deep respiration was significantly smaller ($P<0.05$) and the E/I ratio was significantly lower ($P<0.001$) in the patients.

Response to the Valsalva manoeuvre (Table 5) did not differ significantly between the two groups.

During the sustained isometric exercise (Table 6) blood pressure (Fig. 3) and heart rate (Fig. 4) significantly increased in patients and controls ($P<0.001$). However, in the latter this increase was significantly more marked ($P<0.05$). Two minutes after the end of the isometric exercise the resting values were almost reached, with the exception of diastolic pressure in the patients, which was still increased. Beat-to-beat variation was not significantly different during the whole test in the two groups and the sustained exercise had no significant influence.

Table 1. Autonomic disturbances reported by patients and controls

	Controls ($n=18$)	Patients ($n=22$)	P
Postural dizziness	4	12	<0.05
Fainting	0	4	<0.05
Disturbances of micturition	0	7	<0.05
Bowel dysfunction	4	5	NS
Sleep troubles	5	15	<0.05
Sleeping during the day	2	10	<0.05
Hypersalivation	2	5	NS
Seborrhoea	0	4	<0.05
Increased sweating	1	7	<0.05
Score			
Mean	1.00	3.14	<0.001
SD	0.94	1.83	
Max.	3.00	6.00	
Min.	0.00	0.00	

Table 2. Blood pressure, heart rate and beat-to-beat variation (MCD) at rest. DA = dopamine agonist

	Controls ($n=18$)		All patients ($n=20$)			Patients with DA ($n=13$)			Patients without DA ($n=7$)		
	Mean	SD	Mean	SD	P	Mean	SD	P	Mean	SD	P
Blood pressure (mmHg) (10 min recumbent)											
systolic	143.06	13.56	131.25	20.42	0.0427	125.18	16.50	0.0031	142.10	24.48	NS
diastolic	93.33	8.56	85.58	10.03	0.0146	83.08	8.19	0.0038	90.24	12.07	NS
Heart rate (beats/min) (10 min recumbent)	68.61	9.67	68.18	13.19	NS						
Beat-to-beat variation (ms) (10 min recumbent)	15.68	10.49	15.63	14.70	NS						

Table 3. Postural changes of blood pressure, heart rate and beat-to-beat variation (MCD)

	Controls ($n = 18$)		Patients ($n = 20$)		P
	Mean	SD	Mean	SD	
Blood pressure after tilting (mmHg)					
systolic	134.72	13.77	120.75	21.48	0.0226
diastolic	96.39	12.81	85.75	12.90	0.0146
Blood pressure 5 min after tilting (mmHg)					
systolic	144.44	13.60	127.00	20.42	0.0044
diastolic	98.89	12.43	87.75	12.62	0.0094
Blood pressure change after tilting (mmHg)					
systolic	−8.33	12.13	−10.50	8.45	NS
diastolic	2.50	23.67	−0.17	9.44	NS
Difference 5 min after tilting − at rest (mmHg)					
systolic	1.39	13.11	−4.25	15.09	NS
diastolic	5.56	9.51	2.17	9.55	NS
Heart rate (beats/min)					
after tilting	78.56	11.91	78.60	14.05	NS
5 min after tilting	80.06	14.40	79.80	13.43	NS
Change of heart rate (beats/min)					
after tilting	9.94	5.58	10.42	5.58	NS
Beat-to-beat variation (ms)					
after tilting	12.29	7.61	9.76	8.49	NS
5 min after tilting	10.41	7.36	11.03	13.33	NS
MCD change after tilting (ms)					
absolute value	3.39	5.88	5.87	9.38	NS
relative to value at rest	0.14	0.37	0.23	0.58	NS
30/15 ratio	1.01	0.07	0.99	0.05	NS

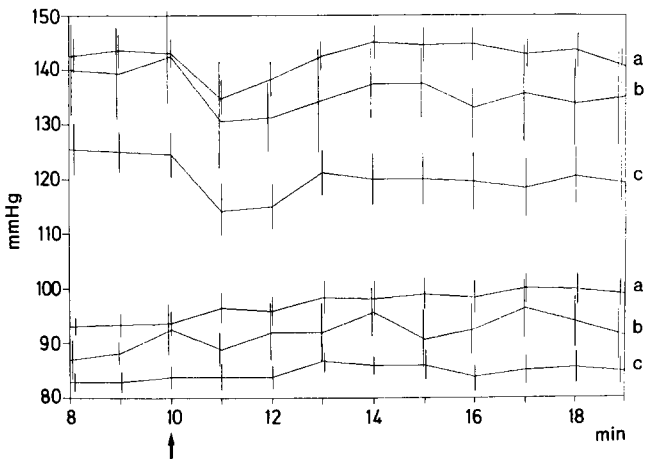

Fig. 1. Systolic (*upper curves*) and diastolic (*lower curves*) blood pressure (mean ± SE) in controls *(a)*, patients without dopamine agonists *(b)* and patients receiving dopamine agonists *(c)* after being brought into a vertical position (↑)

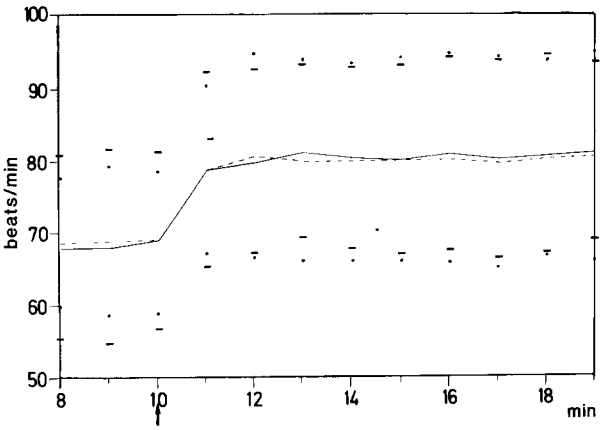

Fig. 2. Heart rate (mean ± SD) in controls and patients after being tilted to 90° head-up (↑); – – – and ·, controls; ——— and –, patients

Discussion

Other authors [1, 3, 21, 27] have reported similar autonomic disturbances to those recorded in the present study. Although many patients complained of dizziness after standing up, no pathological postural drop of blood pressure could be measured. This finding is difficult to explain. It might be that we have missed short-lived changes of blood pressure. This is suggested by the findings of Goetz et al. [12] and of Gross et al. [13], who found a significantly greater drop in blood pressure in parkinsonian patients than in controls immediately after tilting. When considering the absolute values given in the paper by Gross et al. [13], which show an immediate postural decrease of mean arterial pressure of 17 and 12 mmHg respectively, it becomes obvious that this difference is not very impressive.

Table 4. Beat-to-beat variation (MCD) and E/I ratio during deep respiration

	Controls ($n = 18$)		Patients ($n = 21$)		P
	Mean	SD	Mean	SD	
Beat-to-beat variation during deep respiration (MCD) (ms)	27.12	11.70	18.07	14.51	NS
Increase of MCD during deep respiration (ms)	10.51	13.37	0.05	4.48	0.0021
E/I ratio	1.22	0.10	1.10	0.08	0.0007

Table 5. Valsalva ratios

	Controls			Patients			P
	Mean	SD	n	Mean	SD	n	
Mean Valsalva ratio							
40 mmHg	1.48	0.22	16	1.43	0.30	9	NS
20 mmHg	1.39	0.19	18	1.29	0.21	20	NS
Greatest Valsalva ratio							
40 mmHg	1.55	0.21	16	1.49	0.32	9	NS
20 mmHg	1.45	0.22	18	1.34	0.22	20	NS

Table 6. Blood pressure, heart rate and beat-to-beat variation (MCD) during isometric exercise

	Controls ($n = 17$)		Patients ($n = 21$)		P
	Mean	SD	Mean	SD	
Blood pressure at rest (mmHg)					
systolic	138.63	10.36	124.44	11.67	0.0006
diastolic	92.16	7.09	83.33	8.55	0.0020
Blood pressure after 5 min isometric exercice (mmHg)					
systolic	175.00	19.20	143.10	19.78	0.0001
diastolic	117.65	12.76	97.38	14.88	0.0002
Blood pressure 2 min after isometric exercise (mmHg)					
systolic	141.18	11.11	126.91	15.53	0.0033
diastolic	91.47	9.31	86.91	10.90	NS
Increase of blood pressure during exercise (mmHg)					
systolic	36.37	15.31	18.65	14.56	0.0012
diastolic	25.49	10.27	14.05	10.63	0.0022
Heart rate (beats/min)					
at rest	68.06	10.28	70.43	11.15	NS
after 5 min isometric exercise	84.88	14.60	80.00	11.66	NS
2 min after isometric exercise	68.71	11.42	71.33	13.00	NS
Increase of heart rate (beats/min)					
during isometric exercise	16.82	13.86	9.11	4.75	0.0310
Beat-to-beat variation (ms)					
at rest	17.48	11.06	14.17	9.61	NS
during isometric exercise	14.95	8.11	12.66	11.03	NS

Turkka et al. [27] also reported a normal postural drop in blood pressure measured with a sphygmomanometer in patients with Parkinson's disease, although the corresponding increase of serum noradrenaline was diminished. When measuring blood pressure intra-arterially, Appenzeller and Goss [2] found no pathological postural drop in a group of nine patients suffering from Parkinson's disease; one other patient had marked postural hypotension.

Beat-to-beat variation is under vagal control at rest; its strongest stimulus is deep respiration [9]. At rest we measured normal values but the response to deep respiration was clearly reduced in our patients with idiopathic Parkinson's disease. The Valsalva manoeuvre first results in tachycardia and vasoconstriction and subsequently to bradycardia and a decrease of blood pressure. This response is under complex parasympathetic and sympathetic control [8]. The Valsalva ratio,

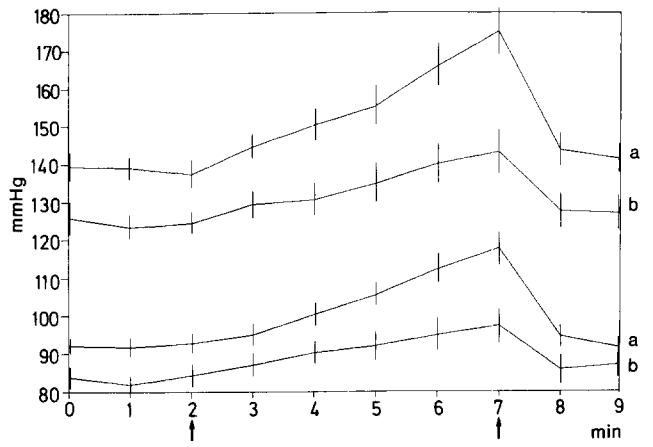

Fig. 3. Systolic (*upper curves*) and diastolic (*lower curves*) blood pressure (mean ± SE) in controls *(a)* and patients *(b)* during isometric exercise from ↑ to ↑

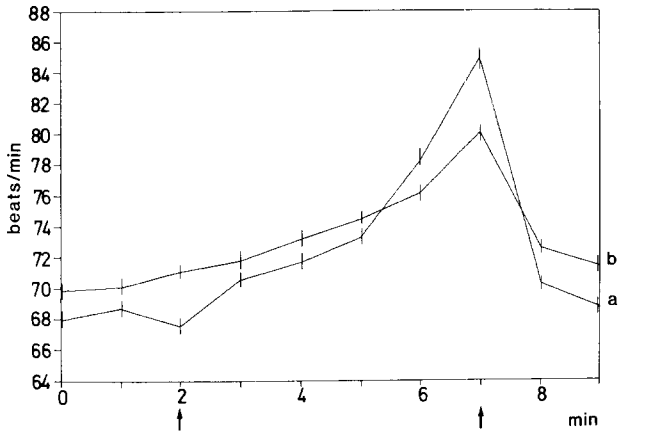

Fig. 4. Heart rate (mean ± SE) in controls *(a)* and patients *(b)* during isometric exercise from ↑ to ↑

which is a measure of the heart rate changes, was normal in our patients. Gross et al. [13] also found no significantly different Valsalva ratio between parkinsonian patients and controls. A reduced blood pressure response in patients with Parkinson's disease has been reported by Appenzeller and Goss [2]. As mentioned above, it was not possible to monitor the blood pressure changes during the present study.

Sustained isometric exercise leads to an increase in heart rate and blood pressure when the sympathetic pathways are operative [9]. Our patients with idiopathic Parkinson's disease had a significantly diminished heart rate and blood pressure response, which points to damage of sympathetic pathways.

Resting blood pressure is normal in idiopathic Parkinson's disease, and levodopa as well as anticholinergics have no noticeable effect on it [12, 13]. However, in our patients dopamine agonists led to a significant reduction of resting blood pressure. This is in agreement with the findings of Reid and Bateman [22] and of Montastruc et al. [17]. The latter authors described a normalization of blood pressure, but no influence on heart rate, in hypertonic patients suffering from Parkinson's disease and taking bromocriptine. According to Mehta and Tolis [16] bromocriptine-induced hypotension is secondary to arterial and venous relaxation. Apart from this reduction of resting blood pressure induced by dopamine agonists, antiparkinsonian treatment probably had no significant influence on the results of the present study. Appenzeller and Goss [2] and Gross et al. [13] were unable to find differences in cardiovascular responses between untreated parkinsonian patients and those taking levodopa and anticholinergics. Goetz et al. [12] found no difference when examining the patients before and after a dose of levodopa.

In conclusion, in our patients with idiopathic Parkinson's disease we found normal blood pressure, normal heart rate and normal beat-to-beat variation at rest; blood pressure and heart rate response to postural change did not differ significantly from the control values. It cannot, however, be ruled out that short-lived changes have been missed. From our results and from a review of the literature it seems that a marked orthostatic hypotension only occurs in exceptional cases of idiopathic Parkinson's disease and that the postural response is not significantly influenced by modern drug treatment. Dopamine agonists, however, induce a significant reduction of systemic blood pressure.

The normal response of blood pressure and heart rate to posture as well as the normal heart rate response to the Valsalva manoeuvre point to an operating peripheral autonomic reflex arc [4, 11]. On the other hand, blood pressure and heart rate responses to sustained isometric exercise and to deep respiration were clearly pathological. It is likely that this was due to damage to the central part of the autonomic reflex arcs, as already suggested by Gross et al. [13]. It is well known that patients suffering from idiopathic Parkinson's disease may have lesions in the hypothalamus and in the locus coeruleus [18, 20, 24], both of which are involved in central autonomic regulation. Furthermore, it is well known that the disturbed metabolism of catecholamines plays a prominent role in the pathophysiology of Parkinson's disease [23]. Catecholamines are the most important neurotransmitters in the central part of the autonomic nervous system. Thus it is likely that the above-mentioned morphological findings are responsible for the pathological response of blood pressure and heart rate to sustained isometric contraction and to deep respiration.

In the light of our findings it is very unlikely that the autonomic disturbances in idiopathic Parkinson's disease and in progressive autonomic failure are simply different aspects of a single spectrum. In the latter pathological postural responses and pathological findings with regard to Valsalva manoeuvre are predominant findings [5, 6], which were both normal in our patients.

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